Incorporating a Generic Model of Subcutaneous Insulin Absorption into the AIDA v4 Diabetes Simulator

1. A Prospective Collaborative Development Plan

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Abstract

Introduction:

AIDA v4 is an interactive educational diabetes simulator that has been made available, for over a decade, without charge via the Internet. The software is currently freely accessible at http://www.2aida.org. This report sets out a collaborative development plan to enhance the program with a new model of subcutaneous insulin absorption, which permits the simulation of rapidly acting and very long-acting insulin analogues, as well as insulin injection doses larger than 40 units.

Methods:

A novel, generic, physiological subcutaneous insulin absorption model is overviewed and a methodology is proposed by which this can be substituted in place of the previously adopted insulin absorption model utilized within AIDA v4.3a. Apart from this substitution it is proposed to retain the existing model of the glucoregulatory system currently used in AIDA v4.3a.

Results:

Initial simulation results based on bench testing of this approach using MATLAB are presented for the exogenous insulin flow profile (I_{ex}) following subcutaneous injections of a rapidly acting insulin analogue, a short-acting (regular) insulin preparation, intermediate-acting insulins (both Semilente and neutral protamine Hagedorn types), and a very long-acting insulin analogue.

Discussion:

It is proposed to implement this collaborative development plan—first by bench testing the approach in MATLAB and then by integrating the generic subcutaneous insulin absorption I_{ex} model into the AIDA simulator in Pascal. The aim is to provide enhanced functionality and educational simulations of regimens utilizing novel insulin analogues, as well as injections larger than 40 units of insulin.

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Abbreviations: (BG) blood glucose, (I_{ex}) exogenous insulin flow profile, (IU) international units [of insulin], (NPH) neutral protamine Hagedorn

Keywords: absorption, computer, diabetes, insulin, model, simulation, software

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Introduction

Proper management of chronic illness is frequently a complex problem with multiple, and often competing, priorities. Patients with diabetes should, for example, meticulously balance food intake, exercise, insulin delivery, and other lifestyle factors known to affect blood glucose (BG) levels. It is now apparent that existing standards of diabetes care are not sufficient, as tightening glycemic control really makes a difference to patient well-being and future prospects.[1] Planning and implementing proper control are complicated by the fact that each patient's care must be designed afresh with reference to the patient's unique biology and personal circumstances.

How should clinicians and patients learn how much and which type of insulin to give and when—how to restrict carbohydrate loads via meals—or what happens if a patient misses a meal or eats more than usual? Such questions are even more relevant, as diabetes mellitus presently is estimated to affect over 150 million people worldwide.[2] However, the incidence of the disease is increasing rapidly with over 220 million people expected to have the disease worldwide by 2010 and over 300 million by 2025.[3,4] A group from the Centers for Disease Control in Atlanta, Georgia, estimated that by 2050 there will be 48 million people diagnosed with diabetes in the United States alone.[5]

Health-care professionals acquire some of their knowledge during training and postgraduate continuing medical education courses, but a large part of their skills derives from their own unique experience. Medical practice involves learning through the whole of one's working life. This process has traditionally involved modalities such as clinical rounds, educational meetings, conferences, refresher courses, seminars, lectures, workshops, and symposia. Unfortunately, these modalities are often ineffective in mediating improvements in patient care through changes in physician behavior.

Patients with chronic diseases also learn from their own care. Experienced diabetic patients are supposed routinely to increase and decrease their daily insulin dosage in response to their daily diet and exercise patterns, and clinical data they collect using their glucometer. Clearly it is not ideal, however, to learn about diabetes control solely from real-life experiences because of the long time frames involved, aside from the possible dangers of hypo- or hyperglycemia. Efficient and safe ways are needed to learn and practice how such adjustments should be made.

Education is difficult if based only on verbal and written presentations of dry facts. The aim should also be to teach diabetes self-management in an intuitive and enjoyable way so that the knowledge can be enduring. In the same way that aircraft pilots and air traffic controllers are trained for routine and emergency procedures on airplane and air traffic simulators, it should be possible for diabetic patients to be trained to make physiologically appropriate responses using a diabetes simulator—in absolute safety and in a relatively short space of time. The AIDA v4 diabetes simulator is a good example of allowing users to experiment with virtual patients without any risk.[6]

The AIDA system has been in widespread general use for more than a decade[7,8] and has been positively assessed by a wide variety of different types of users.[9] Nevertheless, a large number of requests have been received over this period arising from developments in medical technologies (e.g., insulin analogues, new oral hypoglycemic agents), as well as computer developments (e.g., 32/64-bit Windows operating systems and graphical user interfaces).[10,11]

It is important to stress that the major need is not just about creating a Windows version of the program with a more user-friendly graphical user interface instead of the current DOS version, but that important enhancements in *content* also need to be considered to address some of the recently reported requests received from an *n* = 200 survey of AIDA users.[12] Such desired enhancements include, for example, the provision of oral hypoglycemic agents, proper inclusion of diurnal variations, and adding new insulin analogues to the program in order to permit the simulation of any insulin management regimen currently used in clinical practice.

As a first stage to updating the AIDA simulator, a decision has been taken that revisions will commence with extending the types of insulin preparations the program is able to handle. A large number of insulin formulations are available to treat diabetic patients. The current version of the AIDA v4 software architecture has a limit of four different types of insulin—short-acting (regular) insulin, intermediate-acting insulin [Lente type and neutral protamine Hagedorn (NPH) type], and long-acting insulin (such as Ultralente)—that can be catered for within the program, with any two preparations being injected at a given time. Since the late 1990s, insulin analogues have also been adopted into widespread clinical practice, and these also now need to be incorporated.

It is envisaged to produce an updated release of AIDA (v4.5) that will cover rapidly acting insulin analogues (e.g., Humalog or Aspart), short-acting (regular) insulin, intermediate-acting insulin (Semilente type and NPH type), and very long-acting insulin analogues (e.g., glargine, Lantus, or detemir), as well as premixed biphasic insulin preparations involving combinations of rapidly acting analogues and intermediate-acting insulin, such as Humalog Mix 75/25, Humalog Mix 50/50, and NovoLog Mix 70/30.

These types of preparations were among the "wish list" features requested by users for a new release of AIDA.[12] Such extensions clearly require modifications and revisions to the insulin part of the model underlying the simulator program. For this purpose, a generic model of subcutaneous insulin absorption published by Tarín and colleagues[13,14] has been selected to replace the Berger and Rodbard[15] insulin absorption model adopted in the current release of the AIDA software (v4.3a).

Extension of the AIDA program and integration of the new insulin absorption model are overviewed in two parts. This article describes the components currently available that can be combined in order to enhance system functionality. The second part of this article,[16] to be found in a forthcoming issue, will serve to demonstrate how the integrated system may work, along with preliminary simulation results and comparisons between model output from the current and new AIDA educational diabetes simulators.

Methods

Modeling and Simulation as Educational Tools

Computer simulations are not new in nonmedical research and development. Much of climatology and geology is modeled with computers, and engineers routinely design products using mathematical simulations rather than by building and testing prototypes. Today, researchers are increasingly turning to computers and the formalized language of mathematics to explore medical science. The fundamental idea is that if you can model a real thing on a computer, you can answer many questions without experimenting with the real thing. While models are far from perfect because they depend on imperfect information, they can provide an intelligent basis for making decisions when faced with uncertainty.

The literature dealing with mathematical modeling for diabetes is abundant.[17] Mathematical models of varying complexity and formalism (deterministic versus stochastic; continuous versus discrete; using ordinary differential equations, partial differential equations, optimal control theory, integral equations, matrix analysis, etc.) have been proposed and described in the literature.[18] The proposed aims underlying these different models also exhibit a large variety of intended uses. Some models are planned to describe the evolution from diabetes without complications to the stage of diabetes with complications in order to show that prevention of complications would improve people's quality of life and reduce costs to the national health and social services. For example, Archimedes is a very detailed, comprehensive, continuous person-by-person, object-by-object simulation model, spanning from biological details to the care processes, logistics, resources, and costs of health-care systems.[19]

The majority of mathematical models proposed in the diabetes literature, however, have been restricted to the description of the dynamics of glucose–insulin interaction. These models provide insights; improve intuitions; clarify assumptions for formal theory; allow for planning studies, estimating parameters, determining sensitivities, and simulating simple and complex phenomena; and provide future predictions. However, making such models accessible to a large number of users has not been achieved too widely, except perhaps with simulation programs such as AIDA.[20]

Overview of AIDA

In a similar way to a flight simulator, which is based on a more-or-less realistic model of a plane, there is a model of the human body behind the AIDA diabetes simulator that reflects underlying physiological control processes involving glucose and insulin as two chemical substances.[21,22] External variables to the model include foods and insulin preparations.[23] The AIDA model contains a limited set of parameters that reflect metabolic variations among individuals. The aim of the AIDA v4 diabetes simulation approach has been to present in detail each piece of knowledge that went into development of the model (e.g., see http://www.2aida.org/technical for further information), making the resulting simulation tool available without charge.

The AIDA model consists of interrelated glucose and insulin submodels as shown in **Figure 1**. The glucose model contains a single differential equation that describes the temporal evolution of the concentration of glucose in the blood.[23] Glucose enters the bloodstream via intestinal absorption and hepatic glucose production. Stress (not seen in **Figure 1**) could also be considered as a factor elevating the blood sugar level. Glucose is removed from

the extracellular space by utilization in the various organs and tissues (liver and periphery) and by renal excretion above the renal threshold. Exercise (not illustrated in **Figure 1**) could also be considered as contributing to the removal of glucose from the blood to muscle tissues. The different glucose fluxes are usually computed as complex functions of glucose and insulin levels.[23]

The insulin submodel contains two differential equations that formulate changes in the level of insulin in the plasma and in a fictive ("active") insulin pool that was introduced to mimic the delay in the action of insulin.[15] In patients with insulin-dependent (type 1) diabetes mellitus, only exogenous insulin enters the bloodstream. The time course of insulin absorption into the circulation is described according to the phenomenological model of Berger and Rodbard[15] using insulin preparation-specific parameters.
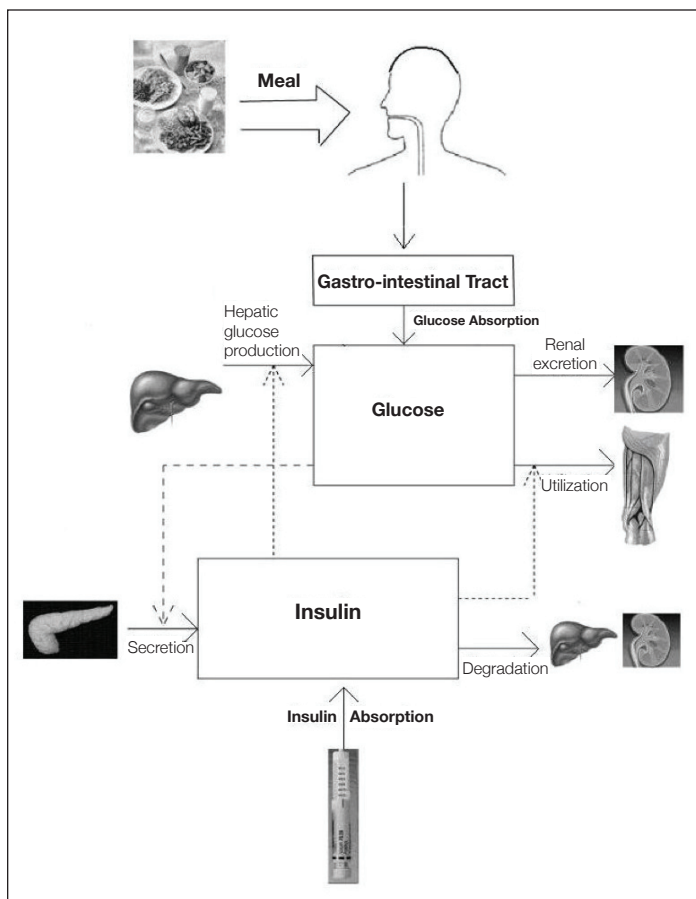

Figure 1. Schematic diagram summarizing the glucose–insulin model with major components highlighted (lifestyle factors omitted). "Secretion," endogenous insulin secretion from the pancreas in noninsulin-dependent (type 2) diabetes mellitus (not currently modeled, but planned for future development). "Degradation," degradation/breakdown of insulin in the liver. Solid lines demonstrate flows. Dashed lines show control actions.

If the insulin regimen consists of more than one injection component, then the overall rate of insulin absorption can be computed by adding together the different contributions of all daily injections and the preparations that they contain.

The AIDA model contains a set of parameters, the values of which were taken from representative references and/or estimated from published experimental and clinical data. Both mathematical expressions specifying model equations and values of model parameters can be found in Lehmann and Deutsch,[23] as well as at the http://www.2aida.org Web site.

For educational purposes, individual virtual diabetic patients are characterized in AIDA by their body weight, renal threshold for glucose, and normalized hepatic and peripheral insulin sensitivities. These sensitivities are considered to vary according to a specified daily diurnal rhythm. These parameters allow patients with different degrees of insulin resistance and various degrees of glycemic impairment to be described and studied.

Users can create potentially unlimited numbers of virtual patients with diabetes and test how different types of treatments, doses and dosing regimens, and even lifestyle (dietary) changes affect the daily BG profile. If a simulated regimen is found unable to keep glycemic levels within desired limits, users can try alternative management regimens that seem to improve this daily pattern.[24] AIDA also attempts to include elements that encourage the practitioner to reflect on each case, and a knowledge-based system is available to suggest changes in the insulin dosage regimen for educational purposes for users unsure what to try simulating next.

Figure 2A shows plasma insulin levels following the subcutaneous injection of various doses of short-acting (regular) and NPH insulin preparations, as calculated by the current AIDA model. These curves clearly reflect both insulin absorption from the subcutaneous depot and insulin disposition/elimination, which follow once insulin has entered the systemic circulation. **Figure 2B** displays the percentage of the injected dose—remaining at the injection site—over time that has not yet been absorbed.

To give some idea of what AIDA can do, **Figure 3A** shows a baseline simulation for "Steven Jones," a "virtual diabetic patient" included in the AIDA database. The clinical information that the user is provided about this "virtual patient" is as follows. "This man is a relatively newly diagnosed insulin dependent (type 1) diabetic patient. He has had problems maintaining his blood glucose profile on two and, more recently, three injections per day, so currently he is controlled on four injections per day. He tends to quite high blood glucose levels in the middle
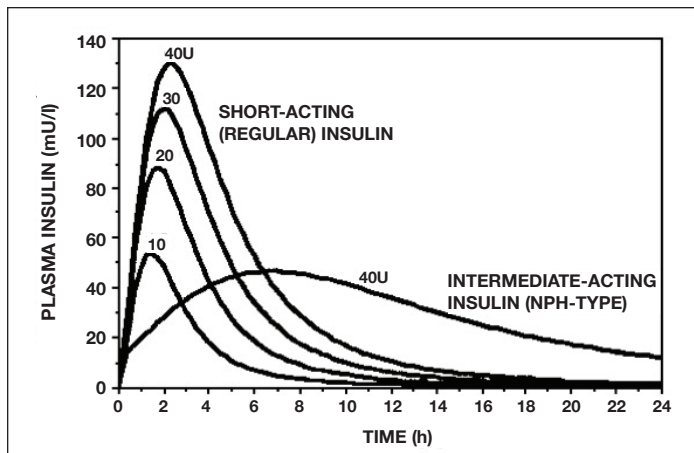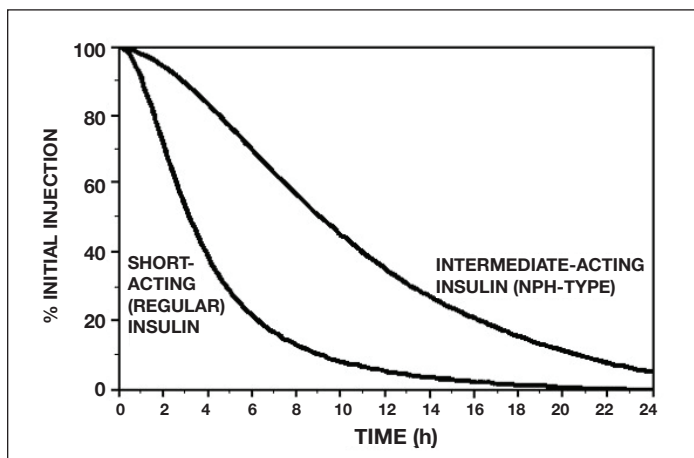
Figure 2A

Figure 2B

Figure 2. (**A**) Insulin absorption graph from the existing AIDA v4.3a program showing plasma insulin levels (in mU/liter) against time from injection for different doses of a short-acting (regular) insulin preparation (e.g., Actrapid-like) and for an intermediate-acting insulin preparation (e.g., NPH- or Monotard-like). (**B**) Insulin elimination graph from the existing AIDA v4.3a program showing the proportion (%) of the initial injected dose of a short-acting (regular) insulin preparation (e.g., Actrapid-like) and an intermediate-acting insulin preparation (e.g., NPH- or Monotard-like) remaining at the absorption site against time from injection.

of the day, despite not eating excessively. Try and see if you can reduce his midday blood glucose levels." The upper graph in **Figure 3A** shows blood glucose information, whereas the lower graph in **Figure 3A** provides a composite display of information regarding insulin and carbohydrate intake. The distribution of meals eaten can be seen on this graph along with the four-times-daily short-acting (regular) Actrapid and intermediate-acting Humulin I insulin regimen that he has been prescribed. Superimposed on these graphs are predicted steady-state BG and plasma insulin profiles as calculated by the AIDA model.[10]

Having performed such a baseline simulation, users can change any of the input variables to simulate the glycemic effects of such changes. For example, a user could simulate what would happen to a hypothetical/virtual patient's BG profile if the morning Humulin I dose was increased by 6 units, if the injection time was moved later, if the bedtime snack was shifted earlier, or if the carbohydrate content of supper was increased by 25 g. A user could transfer the patient to Humulin M3 in place of the previous short- and intermediate acting preparations or perhaps try the case scenario with a "pen regimen," taking a longer-acting insulin preparation at night. The list of possibilities is endless; a near infinite number of simulations can be performed with AIDA.

As shown in **Figure 3A**, the example "virtual diabetic patient" tended to have high BG levels during the day. **Figure 3B** shows the effect on the BG profile of increasing the before-breakfast (7:00 a.m.) intermediate-acting Humulin I dose from 3 to 7 units of insulin. As can be seen, such a change leads to the previously raised BG level during the course of the afternoon being brought more fully under control.[10]

Generic Subcutaneous Insulin Absorption Model

Current insulin formulations can be classified according to their duration of action as rapidly acting insulin analogues (e.g., Lispro, Novorapid, Humalog), short-acting preparations (e.g., regular, Actrapid), intermediate-acting preparations (e.g., NPH, Semilente, Protaphane), and very long-acting insulin analogues (e.g., glargine, Lantus, detemir). Fixed mixtures of short- and intermediate-acting insulin (biphasic insulin) and rapidly and intermediate-acting insulin can also be found. For modeling subcutaneous insulin absorption, many models have been described in the literature. A useful review may be found in Nucci and Cobelli.[25]

However, existing models of subcutaneous insulin absorption usually are unable to properly describe absorption patterns of very long-acting insulin analogues.

In contrast, Tarín and colleagues[13,14] have presented a novel, comprehensive, generic subcutaneous insulin absorption model that overcomes these problems. The new model allows the exogenous insulin flow into the bloodstream of each insulin preparation/class to be computed over time depending on the injected insulin dose. This approach is based on the model described by Trajanoski and co-workers,[26] which itself is a simplification of the model of Mosekilde and colleagues.[27] In contrast to the model of
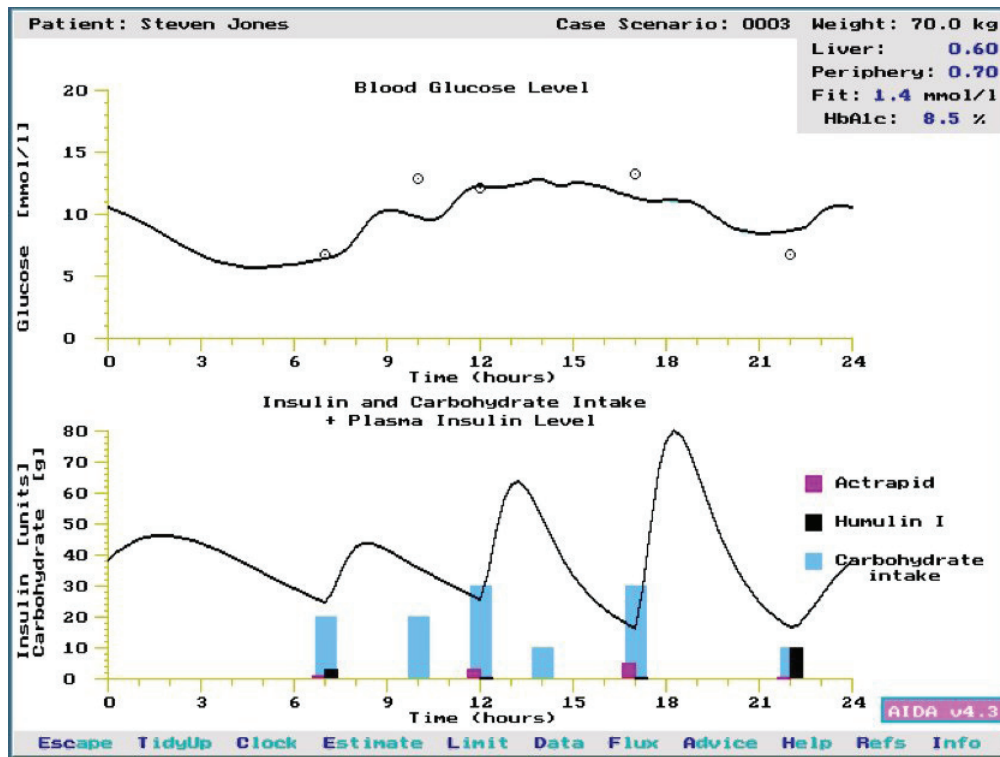
Figure 3A

Figure 3B

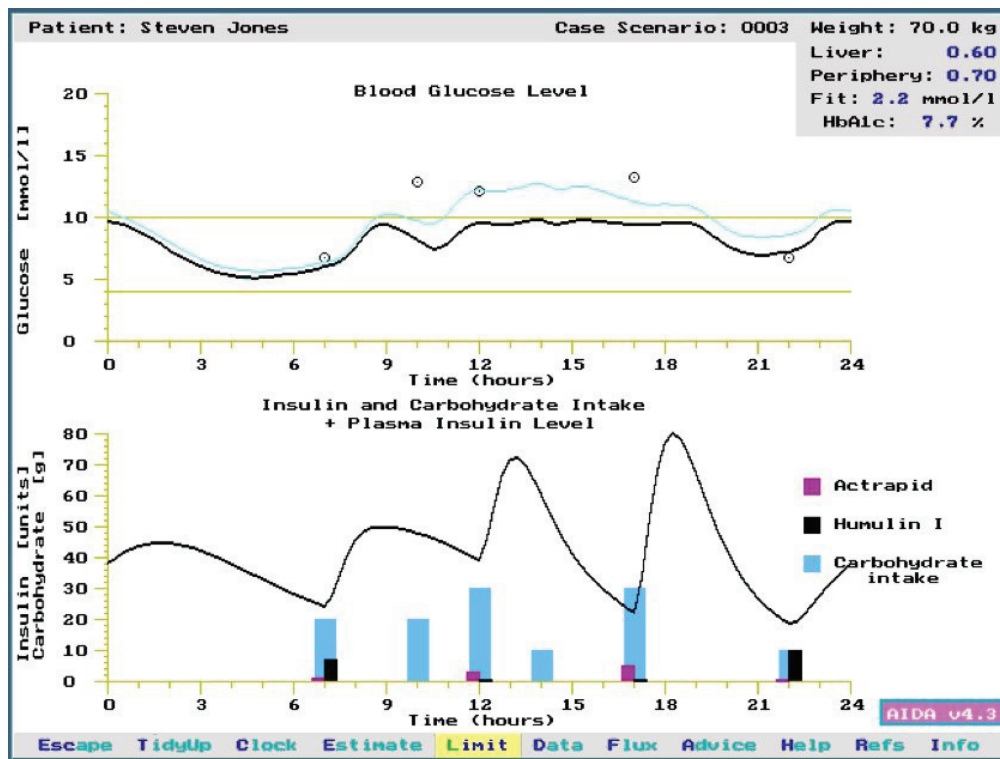**Figure 3.** (**A**) Baseline 24-hour simulation from the AIDA interactive educational diabetes simulator for an example patient with insulin-dependent (type 1) diabetes mellitus on a four-times-daily short-acting (regular) Actrapid and intermediate-acting Humulin I insulin regimen. (Bottom) Insulin and carbohydrate intake with a predicted 24-hour plasma insulin curve. (Top) Predicted 24-hour blood glucose profile computed on the basis of insulin and carbohydrate intake. Case derived from Lehmann.[10] (**B**) The effect on the blood glucose curve shown in A of increasing the before-breakfast (7:00 a.m.) intermediate-acting Humulin I dose from 3 to 7 units of insulin. As can be seen, such an adjustment leads to the previously raised blood glucose level during the course of the afternoon being brought more fully under control. Case derived from Lehmann.[10]

Trajanoski *et al.*,[26] where only two different association states for insulin were considered—hexameric and dimeric—a bound insulin state is adopted in the current model.[13] This allows for the consideration of decreased solubility at physiological pH and insulin precipitation or crystallization of very long-acting analogues, such as insulin glargine, which delay absorption. The approach has been validated using data from the literature.[28,29]

As the concentration of each insulin component varies over both time, t, and space (distance from the injection site, r), the model is described by the following system of partial differential equations:

$$\frac{\partial c_d(t,r)}{\partial t} = P\big(c_h(t,r) - Qc_d(t,r)^3\big) - B_d c_d(t,r) + D\nabla^2 c_d(t,r)$$

$$\frac{\partial c_h(t,r)}{\partial t} = -P\big(c_h(t,r) - Qc_d(t,r)^3\big) + \kappa c_b(t,r)(c_{h,\max} - c_h(t,r)) + D\nabla^2 c_h(t,r)$$

$$\frac{\partial c_b(t,r)}{\partial t} = -\kappa c_b(t,r)(c_{h,\max} - c_h(t,r)) + d_b D\nabla^2 c_b(t,r)$$

$$I_{ex}(t) = B_d \int_{V_{sc}} c_d(t,r)dV$$

where c_d, c_h, and c_b stand for dimeric, hexameric, and bound insulin concentrations, respectively.

The spatial and temporal changes in insulin concentrations are determined by transport processes (diffusion from the injection site and absorption into the bloodstream) and chemical reactions involving different forms of insulin.

Insulin is considered to diffuse from the injection site isotropically, i.e., homogeneously and with rotational symmetry with respect to the origin (the injection site). The resulting diffusion volume, V_{SC}, will thus be a sphere with its center at the injection site. This is reflected in the model by the terms $D\nabla^2 c_d(t,r)$, $D\nabla^2 c_h(t,r)$, and $d_b D\nabla^2 c_b(t,r)$ for the dimeric, hexameric, and bound insulin states, respectively. The multiplying factor is the diffusion constant, and the operator ∇^2 stands for the Laplace operator. Dimeric and hexameric insulins are considered to have the same D diffusion rate constant, whereas bound insulin diffuses more slowly $(d_b \in [0,1])$.

Insulin profiles are substantially affected by chemical reactions between different insulin forms. The conversion of bound insulin to hexameric form is described by the term $\kappa c_b(t,r)(c_{h,\max} - c_h(t,r))$, where κ is the conversion rate constant. This process is assumed to be inhibited if the concentration of hexameric insulin is higher than $c_{h,max}$. Association/dissociation between hexameric and dimeric forms of insulin is reflected by the term $P(c_h(t,r) - Qc_d(t,r)^3)$ assuming third-order kinetics. P is interpreted as a production rate constant, and Q is the equilibrium constant of this chemical reaction.

The dynamics and intensity of insulin action depend primarily on the kinetics of insulin absorption. In the model, only dimeric insulin is assumed to enter the circulation in significant amounts. The overall rate of insulin absorption is given by the last equation of the model in which B_d represents the absorption rate constant of dimeric insulin and V_{SC} is the subcutaneous volume containing insulin.

The generic insulin absorption model parameters for different insulin classes are given in **Table 1**.

As the model equations cannot be solved in closed form, numerical integration is required, involving discretization of variables in both *time* and *space*. For time discretization the Euler method[30] with a time step of 0.01 min is used. The spherical diffusion volume is divided into n shells of equal volume, as shown in **Figure 4**. The number of shells to be considered depends on the insulin class and injected insulin dose, as reported by Tarín and colleagues.[14] Outside the outermost shell, the insulin concentration is considered to be nil.

The volume of individual shells is set to be equal to the injected volume.[26] This is calculated from the injected dose and concentration of the preparation used. For instance, if the injected dose is 20 IU and the insulin concentration is 100 IU/ml, the volume of the shell will be 0.2 ml and the radius of the innermost shell will be 0.3628 cm.

Initially the innermost shell contains the total injected dose (and thus the concentration equals that of the preparation administered). This is shown in **Figure 5A**, where the x and y axes represent a section of the shells and the z axis represents insulin concentration. As time goes on, insulin diffuses through the shells and is absorbed (**Figure 5B**).

Numerical integration of the generic subcutaneous insulin absorption model has been carried out using MATLAB.

Results

This section presents some preliminary results using the generic insulin absorption model. **Figure 6** shows the exogenous insulin flow profile, I_{ex}, into the bloodstream as a function of time after subcutaneous injection of 20 IU of different currently used insulin preparations. Clearly, the rapidly acting insulin analogue shows a much higher and earlier peak than the short-acting (regular) insulin. The intermediate-acting insulins (both Semilente type and NPH type) show a pronounced peak, whereas the very long-acting insulin analogue exhibits an almost flat profile.

Table 1.
Model Parameters of the Generic Subcutaneous Insulin Absorption Model for Different Insulin Classes/ Preparations: Q, Hexameric–Dimeric Equilibrium Constant; D, Diffusion Rate; B_d, Absorption Rate of Dimeric Insulin; κ, Bound–Hexameric Conversion Rate; $c_{h,max}$, Bound–Hexameric Conversion Saturation Constant; d_b, Reduction Factor of Bound Diffusion Rate

Parameter Insulin class	Q [ml^2 IU^{-2}]	D [cm^2 min^{-1}]	B_d [min^{-1}]	κ [ml IU^{-1} min^{-1}]	$c_{h,max}$ [IU ml^{-1}]	d_b
Rapidly acting	4.75e-4	3.36e-4	2.36e-2	-	-	-
Short acting (regular)	1.9e-3	8.4e-5	1.18e-2	-	-	-
Intermediate acting (Semilente type)	7.6e-2	8.4e-5	1.18e-2	-	-	-
Intermediate acting (NPH type)	3.04	8.4e-5	1.18e-2	-	-	-
Very long acting	3.04	8.4e-5	1.18e-2	0.01	15.0	0.1

As can be seen, the onset time of the different insulin formulations varies substantially, with the rapidly acting insulin analogue showing the shortest onset time. Five hours after subcutaneous injection, the rapidly acting insulin analogue is fully absorbed, whereas the very long-acting insulin analogue has not even reached its maximum.

Figure 7A depicts the exogenous insulin flow profile, I_{ex}, over time after subcutaneous injection of different doses of short-acting (regular) insulin compared to 40 IU of intermediate-acting NPH-type insulin. I_{ex} data show a peak approximately 1.5 hours after subcutaneous injection for regular insulin, independently of the administered dose, whereas I_{ex} peaks approximately 7 hours after the injection when the intermediate-acting insulin (NPH type) is administered. It is noted that these insulin absorption curves are very similar to the plasma insulin profiles shown in **Figure 2A**, as insulin distribution and elimination do not distort the temporal pattern according to which insulin enters the systemic circulation.

The percentage of insulin dose still remaining at the injection site versus time after subcutaneous injection for short-acting (regular) insulin and intermediate-acting insulin (NPH type) is compared in **Figure 7B**. For short-acting (regular) insulin after 2 hours, 50% of the injected insulin is already absorbed, whereas for intermediate-acting insulin (NPH type), the 50% value is achieved only after 7 hours. After 4.5 hours, 90% of the injected short-acting (regular) insulin is absorbed from the injection site, whereas for intermediate-acting insulin (NPH type), this absorption quota is only observed after 13 hours. The shape of these curves computed by the generic subcutaneous insulin absorption model should be compared with the shape of the curves shown in **Figure 2B** for comparable data from the existing AIDA v4.3a model.
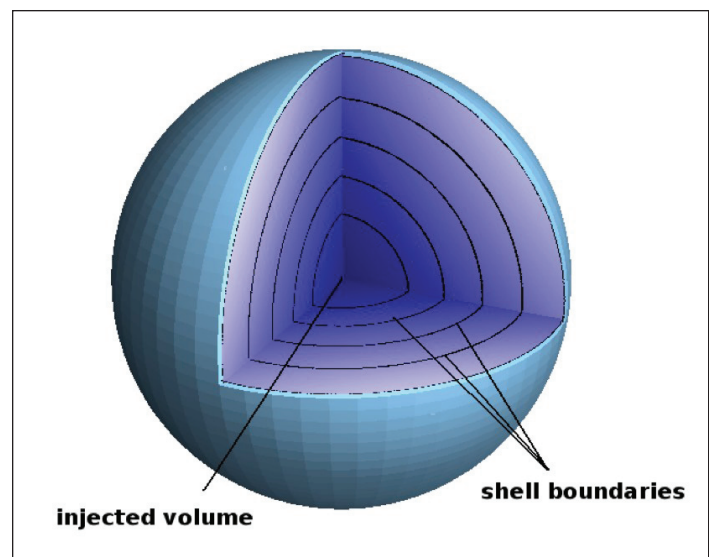

Figure 4. The diffusion volume following a subcutaneous insulin injection is considered to be a sphere discretized in concentric shells of equal volume.

Figure 8A shows the exogenous insulin flow profile, I_{ex}, for different doses of a rapidly acting insulin analogue. Independently of the administered dose, the peak value of I_{ex} appears 0.3 hours after injection. **Figure 8B** shows the exogenous insulin flow profile, I_{ex}, for different doses of intermediate-acting insulin (Semilente type). It can be observed that almost no insulin is remaining 15 hours after the subcutaneous injection. **Figure 8B** also shows that the peak value for the exogenous insulin flow, I_{ex}, is located 2.5 hours after subcutaneous injection. **Figure 8C** shows the exogenous insulin flow for different doses of a very long-acting insulin analogue. As can be seen, during the 24 hours after injection the exogenous insulin flow shows an almost flat profile. The very slow dynamics of the absorption process lead to a greater difference between dosages, such that for lower doses, 24 hours after injection,
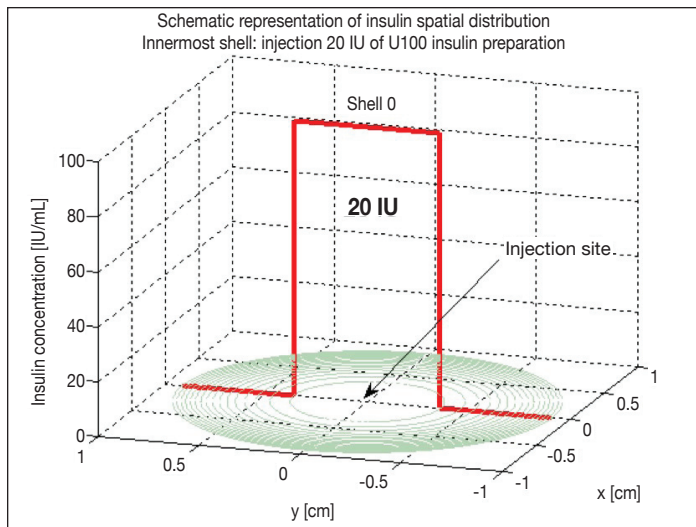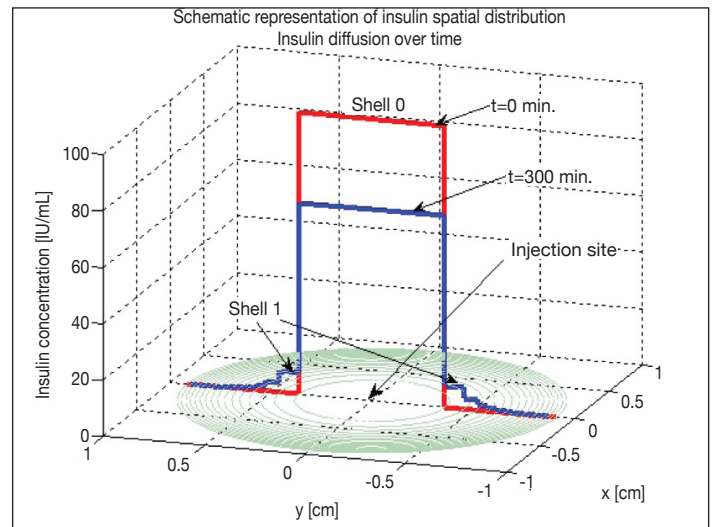
Figure 5A

Figure 5B

Figure 5. Representation of the spatial distribution of insulin at a fixed time. For the model simulation, the diffusion sphere is discretized in a number of concentric shells of equal volume, as shown in Figure 4. If a section in any direction is done, the concentric shells will result in two-dimensional annuli as shown. Because of the homogeneity assumption inside a shell, these annuli stand for the shells, facilitating graphical representation. The x and y axes represent a section of the diffusion sphere, whose center corresponds to the injection site. The z axis represents the insulin concentration at each annulus (and thus each shell). (**A**) The radius of the innermost shell (shell 0) is calculated so that initially it contains the whole insulin dose. An initial concentration of shell 0 will then be that of the insulin preparation. An example for an injection of 20 IU of a U100 insulin preparation is shown. (**B**) As time goes on, insulin diffuses from shell 0 to neighboring shells and is absorbed.

almost all the insulin is absorbed, whereas for higher doses it is not until 36 hours after injection that the insulin is absorbed.

Figure 8D illustrates the percentage of insulin remaining at the injection site versus time after subcutaneous injection of a rapidly acting insulin analogue, intermediate-acting insulin (Semilente type), and a very long-acting insulin analogue. This graph, together with the curves shown in **Figure 7B**, provides a complete overview of the percentage of insulin remaining at the injection site for the main classes of insulin preparations catered for in the generic subcutaneous insulin absorption model.

Discussion

While AIDA v4 is a widely used diabetes simulator,[7,8] which has been available for over a decade, it does have certain limitations.[12] These have been highlighted over the years by different users, but the authors themselves have also been considering how the diabetes simulator should be revised and extended in response to developments in diabetes and computing technology that have taken place over the past ten years. Early general ideas about future developments with the diabetes simulation approach have appeared elsewhere,[24,31,32] reflecting alternative ways in which such enhancements could be envisaged. How progress can be made from the current stage of usage
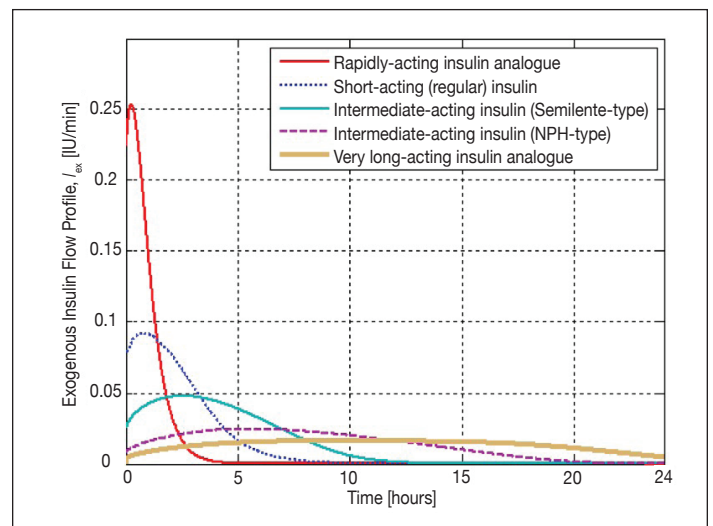

Figure 6. Injections of 20 IU of different insulin formulations: a rapidly acting insulin analogue, a short-acting (regular) insulin, intermediate-acting insulins (Semilente type and NPH type), and a very long-acting insulin analogue. Exogenous insulin flow profile, I_{ex}, is shown in IU/min versus time.

of the software to a more advanced simulator is open to discussion, with one option being to revise the glucose–insulin model itself and another being to focus on the existing inputs of the model, which include variables (insulin and dietary regimen), whereby proper glycemic control can be achieved.
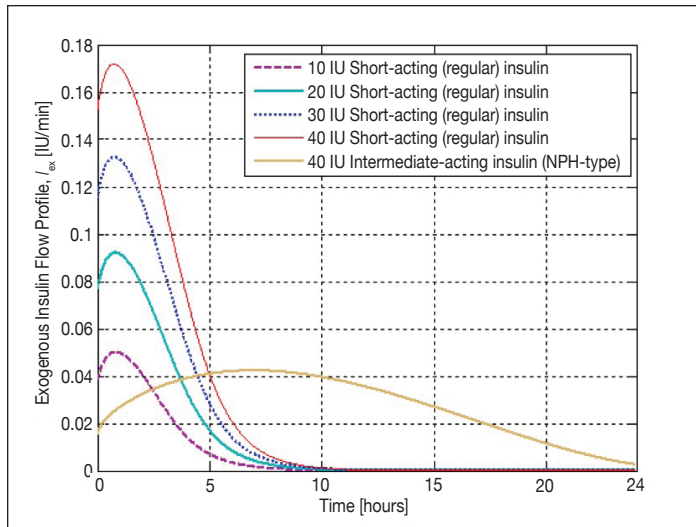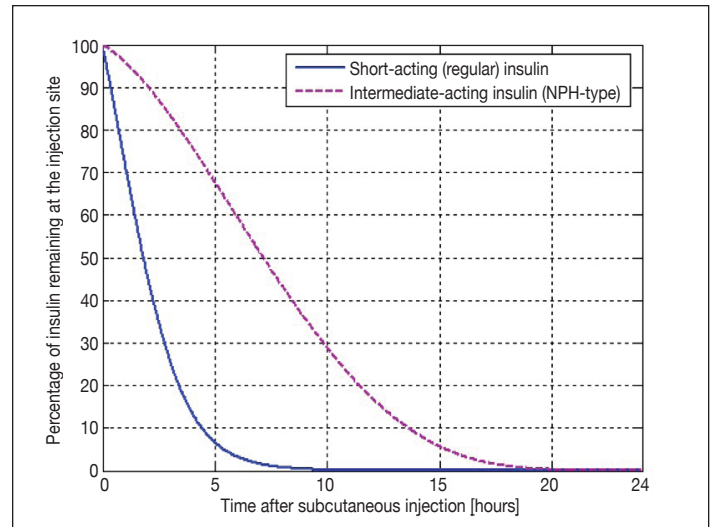
Figure 7A

Figure 7B

Figure 7. (**A**) Injection of different doses of short-acting (regular) insulin (10, 20, 30, and 40 IU) and a 40 IU intermediate-acting insulin (NPH type). The exogenous insulin flow profile, I_{ex}, is shown in IU/min versus time. The shape of these curves for insulin absorption data from the novel, generic subcutaneous absorption model can be compared with the shape of the curves shown in **Figure 2A** for plasma insulin data (absorption and kinetics/elimination data combined) from the existing AIDA v4.3a model. (**B**) Percentage of insulin remaining at the injection site versus time after subcutaneous injection for short-acting (regular) insulin and intermediate-acting insulin (NPH type) as calculated by the generic subcutaneous insulin absorption model. The shape of these curves arising from the new generic subcutaneous absorption model can be compared with the shape of the curves shown in **Figure 2B** for data from the existing AIDA v4.3a model.

Despite some preliminary plans,[24,31,32] however, the work never happened, and here a much more specific and detailed collaborative action plan is described that specifies how it is intended to overcome some of these limitations in the future.

The new version of the educational diabetes simulator should reflect the complexity of diabetes management, i.e., that regulation of the BG concentration is mainly achieved by the action of three control variables—insulin, meals, and oral hypoglycemic agents—as well as modified by the effects of physical exercise and stress. This implies the need to extend the scope of input variables included in the underlying AIDA glucose–insulin model.

Given that there are literally hundreds of models of the human glucoregulatory system in the literature,[33,34] it is suggested that how to specify the inputs may be a relatively weak point for many of these models, perhaps explaining why many of them have not had a greater impact. Many researchers seem to have chosen to simplify model inputs to make them more manageable. However, this article proposes an alternative approach, namely that it is important not to simplify inputs so much that the resulting model is no longer so medically useful.

More generally speaking, model inputs may in fact be the key to a successful implementation of a novel,

improved glucoregulatory simulator. Inputs such as the insulin regimen and diet, as well as exercise and stress levels, clearly affect the model chosen, with different models offering different levels of complexity. Given this, rather than just developing yet another model of the glucoregulatory system, it is hoped to systematically revise the description of the inputs and the spectrum of inputs catered for by the AIDA model, in this way providing a deeper mathematical description and representation of each input. Therefore, it is suggested that there is a need to specify model inputs in a more rigorous and systematic way to improve simulation results.

In AIDA, glucose absorption following food intake has been described by a physiologically based glucose absorption model involving models of gastric emptying, hydrolysis of polysaccharides, and absorption of glucose molecules. This depth of detail is in sharp contrast with the empirical (phenomenological) relationship adopted to describe insulin absorption following subcutaneous injections.

While useful for relatively simple insulin preparations, this empirical approach was found to be incapable of modeling the absorption of very long-acting insulin analogues that have become widely used by large numbers of diabetic patients. The phenomenological model also had problems simulating the subcutaneous absorption of insulin injection
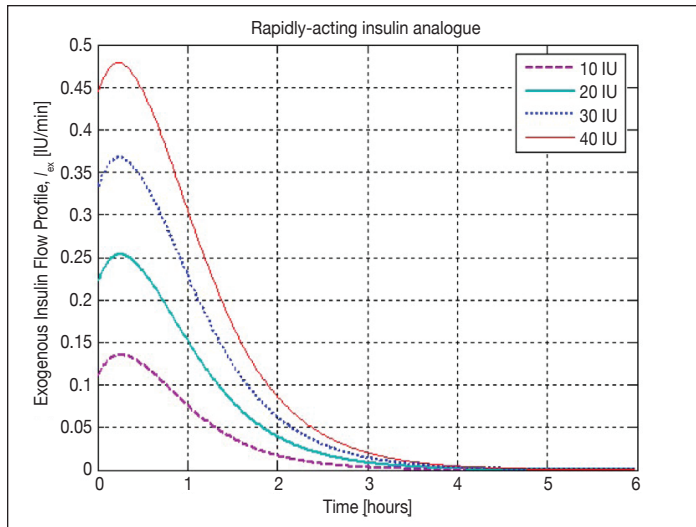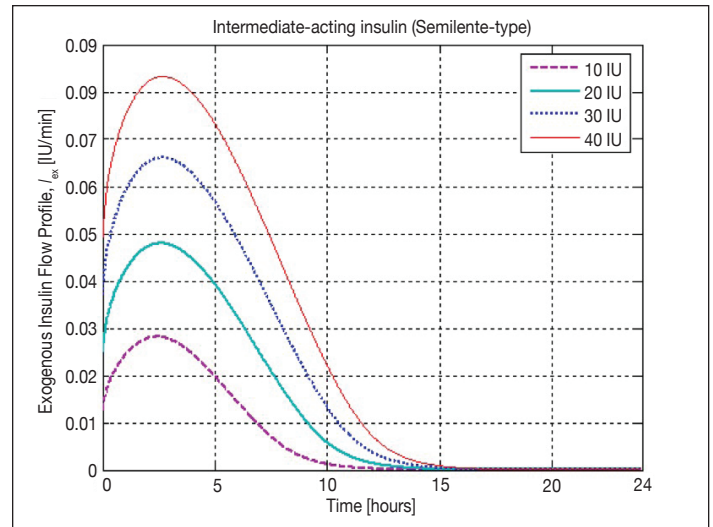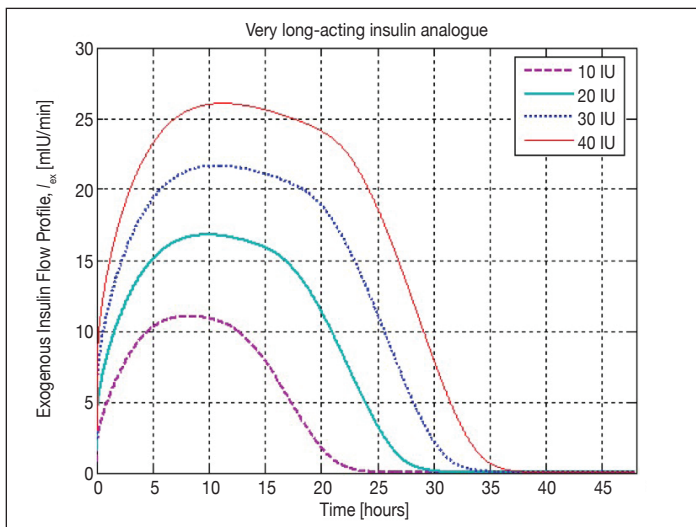
Figure 8A

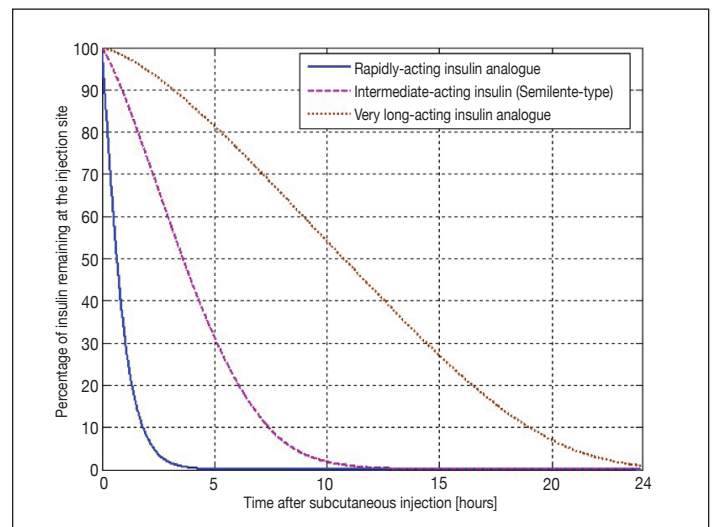
Figure 8B

Figure 8C

Figure 8D

Figure 8. Comparison of injection of 10, 20, 30, and 40 IU for different insulin classes/preparations. The exogenous insulin flow profile, I_{ex} in IU/min is shown versus time for (**A**) a rapidly acting insulin analogue, (**B**) intermediate-acting insulin (Semilente type), and (**C**) a very long-acting insulin analogue. (**D**) Percentage of insulin remaining at the injection site versus time after subcutaneous injection for a rapidly acting insulin analogue, intermediate-acting insulin (Semilente type), and a very long-acting insulin analogue. This graph, together with the curves shown in Figure 7B, provides a complete overview of the percentage of insulin remaining at the injection site for the main classes of insulin preparations considered for inclusion in the new release of AIDA (v4.5).

doses above 40 IU. These limitations have prompted the development of a collaborative action plan during which the restricted empirical insulin absorption model will be substituted by a physiologically based generic subcutaneous insulin absorption model that allows the whole spectrum of available insulin preparations to be catered for within the AIDA program.

Therefore, initially at least for AIDA v4, we aim to retain the same core glucoregulatory model but add a revised subcutaneous insulin input model that offers

a certain elegance and simplicity, along with tangible enhancements to the simulations, without losing what is so good about AIDA. The generic subcutaneous insulin absorption model of Tarín and colleagues[13,14] is planned to be adopted alongside the existing model of insulin kinetics and disposal utilized within AIDA v4 from Berger and Rodbard.[15] This should permit more novel insulin analogues to be simulated by the new software and the current insulin dose limit to be increased above 40 IU per injection.

The 40 IU dose limit within the current release of AIDA (v4.3a) relates to the insulin absorption model applied.[15] The insulin absorption half-life (t_{50}, the time interval to permit 50% of the injected dose to be absorbed) currently adopted within AIDA v4 for intermediate-acting insulin (NPH type) would be too high compared with intermediate-acting insulin (Lente type) and long-acting insulin (e.g., Ultralente) for doses greater than 40 IU of insulin. In contrast, by replacing the insulin absorption model of Berger and Rodbard[15] with the generic insulin absorption model overviewed earlier, no limitations should remain, allowing insulin dosages greater than 40 IU to be modeled successfully.

With the development of an updated version of AIDA v4 incorporating a generic model of subcutaneous insulin absorption, it is also planned to make some further refinements to the AIDA software. Many of these are based on feedback received from users of the existing AIDA v4 program.[12] If possible, the patient weight limit for simulation will be increased above the current restriction of 99 kg. A new upper weight limit of greater than 150 kg is likely to be set.

Other feedback-related upgrades will also be considered, including a plan to increase the carbohydrate content limit per meal that is permitted for simulation, which some diabetic patients have found restrictive.

It is also intended to respond to some technical requests of AIDA users and to resolve certain Turbo Pascal display problems that seem to manifest themselves with the latest generation of notebook personal computers. Finally, the updated version of AIDA v4.5 will be tested with the latest Microsoft Vista operating system to ensure forward compatibility.

What to Expect in the Second Part of This Article?

The second part of this article[16] will present preliminary bench testing results from the application of this collaborative development plan. An analysis will be undertaken of the spatial distribution of insulin in the region of the injection site (the diffusion spheres) for different insulin classes and time instants after the administration of a set dose of insulin. Demonstrations of the proportion of residual insulin in depot versus time after bolus injection will be simulated for different increasing insulin injection volumes and insulin concentrations, as well as to show the different proportions of hexameric, dimeric, and bound insulin over time after a bolus injection. The transformation, diffusion, and absorption processes by which insulin moves from the subcutaneous injection site to the plasma will also be illustrated.

Preliminary data from the integration of the generic subcutaneous insulin absorption model and the currently implemented model in AIDA for insulin kinetics/elimination will also be presented, and comparisons will be made between generic absorption model I_{ex} data and existing absorption data utilized within AIDA v4.3a, highlighting the differences between the approaches. Finally, the methodology to be adopted to actually implement the generic absorption model within AIDA v4 will be overviewed, and the logistical steps required to program this in Pascal will be described.

System Availability

Following completion of the bench testing work we expect a new, improved version of AIDA (v4.5) to become available at the http://www.2aida.org Web site for freeware download and educational use. Readers who wish to be automatically informed by email when the new software is launched are welcome to join the very low volume AIDA registration/announcement list by sending a blank email note to subscribe@2aida.org.

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